

CLAIMS

1. A recognition force microscope for detecting interactions between a probe and a sensed agent on a scanned surface, comprising:
 - a scanning probe having a tip that is sensitive to a property of said surface, said probe adapted to oscillate with a low mechanical Q factor;
 - means for recording the displacement of said probe tip as a function of time; and
 - means for recording both topographic images and the spatial location of interactions between said probe and one or more sensed agents on said surface.
2. A microscope as claimed in claim 1 in which said means for recording the displacement of said probe tip as a function of time comprise a source of radiation directed at said probe, a position sensitive detector that detects radiation reflecting off of said probe, and a controller that processes the detected radiation.
3. A microscope as claimed in claim 1 in which said means for recording both topographical images and the spatial location of binding events between said probe and sensed agents comprises processing circuitry that generates separate topographical and recognition signals.
4. A microscope as claimed in claim 1 in which the amplitude of the upward swing and the amplitude of the downward swing of said probe tip are measured and recorded.
5. A microscope as claimed in claim 1 where the Q factor is 20 or less.
6. A microscope as claimed in claim 1 wherein the probe tip is sensitized with a sensing agent that binds specifically to the sensed agent.

7. A microscope as claimed in claim 6 wherein said sensing agent is an antibody.
8. A microscope as claimed in claim 7 wherein said antibody is tethered by a flexible crosslinker.
9. A microscope as claimed in claim 6 where said sensing agent is tethered by a flexible crosslinker.
10. A microscope as claimed in claim 1 in which said probe includes a magnetic material, and said microscope further includes a time varying magnetic field adapted to excite said probe into motion.
11. A microscope as claimed in claim 4 including an electronic circuit for separating the topographic and recognition signals, said circuit comprising,
 - means for determining the average value of the displacement of said probe on a time scale that is sufficiently long compared to changes caused by topography or binding events such that such events are separately recognized;
 - means for using said average value of said displacement to determine the downward amplitude of said probe from the difference between said average value and the value of the downward displacement;
 - means for controlling the height of said probe, thereby determining the topography using said value of the downward displacement of said probe; and
 - means for determining the value of the upward displacement of the probe from the upward amplitude and said average value of said displacement to generate a signal corresponding to interactions between said probe and said sensed agent on the surface being scanned.

12. A microscope as claimed in claim 4 where the topographic images and the spatial location of binding events are separated by an electronic circuit comprising,

means for digitizing the recorded displacement of said probe tip;

means for determining the average value of the displacement of said probe on a time scale that is sufficiently long compared to changes caused by topography or binding events such that such events are separately recognized;

means for using said average value of said displacement to determine the downward amplitude of said probe from the difference between said average value and the value of the downward displacement;

means for controlling the height of said probe, thereby determining the topography using said value of the downward displacement of said probe; and

means for determining the value of the upward displacement from the upward amplitude and said average value of said displacement to generate a signal corresponding to interactions between said probe and said sensed agent on the surface being scanned.

13. A recognition force microscope for detecting interactions between a probe and a sensed agent on a scanned surface comprising,

a scanning probe having a tip that has been sensitized to a property of said surface, said probe adapted to oscillate with a low mechanical Q factor;

a source of radiation directed at said probe;

a position sensitive detector for detecting radiation reflected from said probe;

a processor for processing signals from said detector to determine both topographic images and the spatial location of interactions between said probe and sensed agents on said surface.

14. A microscope as claimed in claim 13 in which the amplitude of the upward swing and the amplitude of the downward swing of said probe tip are measured and recorded.

15. A microscope as claimed in claim 13 where the Q factor is 20 or less.
16. A microscope as claimed in claim 13 wherein the probe tip is sensitized with a sensing agent that binds specifically to the sensed agent.
17. A microscope as claimed in claim 16 wherein said sensing agent is an antibody.
18. A microscope as claimed in claim 17 wherein said antibody is tethered by a flexible crosslinker.
19. A microscope as claimed in claim 16 where said sensing agent is tethered by a flexible crosslinker.
- 20.. A method of operating an atomic force microscope comprising,
scanning a probe having a tip that is sensitive to a property of a surface of
a sample over said surface while oscillating said probe with a low mechanical Q
factor;
recording the displacement of said probe tip as a function of time; and
simultaneously recording both topographic images and the spatial location
of interactions between the probe and sensed agents on said surface.
21. A method as claimed in claim 20 in which the Q factor is 20 or less.
22. A method as claimed in claim 20 including using the extent of the upward
displacement of said probe tip to measure interactions between said probe tip
and the sample surface.
23. A method as claimed in claim 20 including using the extent of the
downward displacement of said probe tip to control the height of said probe tip
above the sample surface.

24. A method as claimed in claim 20 including using the overall amplitude of said probe tip to control the height of said probe tip above the sample surface.
25. A method as claimed in claim 20 including using the average deflection signal to control the height of said probe tip above the sample surface.
26. A method of screening reagents for binding to a particular target molecule comprising,
 - attaching the target molecule to the tip of a probe and scanning the surface of a sample containing at least one candidate reagent while oscillating said probe tip with a low mechanical Q factor;
 - using the extent of the downward displacement of said probe tip to control the height of the probe above the sample surface; and
 - using the extent of the upward displacement of said probe tip to measure interactions between the target molecule and the candidate reagent.
27. A method as claimed in claim 26 in which the Q factor is 20 or less.
28. A method as claimed in claim 26 including using the tip displacement as a function of time to determine the spatial location of recognition events by comparison to a predicted or recorded displacement pattern generated for the case when there is no recognition.
29. A method as claimed in claim 26 in which candidate reagents are arranged in microtiter wells arrayed on a substrate.
30. A method as claimed in claim 29 including simultaneously recording both topographic images and the spatial location of interactions between the target molecule and the candidate reagents such that recognition events are associated with specific wells.

31. A method of screening ligands for binding to a particular target on a cell surface comprising,

attaching the ligand to the tip of a probe and scanning said cell surface while oscillating said probe tip with a low mechanical Q factor; and

using the extent of the downward displacement of said probe tip to control the height of the probe above the sample surface; and

using the extent of the upward displacement to measure interactions between the target on the cell surface and the ligand.

32. A method as claimed in claim 31 in which the Q factor is 20 or less.

33. A method as claimed in claim 31 including using the tip displacement as a function of time to determine the spatial location of recognition events by comparison to a predicted or recorded displacement pattern generated for the case when there is no recognition.

34. A microscope for detecting surface topography simultaneously with probe-surface interactions, said microscope comprising:

means for causing the probe to sample distance to vary with time rapidly as compared to the time to move the probe over the surface,

means for detecting the peak amplitude of probe motion at each cycle of variation of probe to sample distance,

means for recording the surface topography based on the average amplitude of motion of the probe in relation to said surface, and

means for recording variations in the peak amplitude of probe motion as a function of the probe position over the surface.